Special Issue ITI

From anthropologists' point of view, the emergence of tool use was a revolutionary event in the development of mankind. Did the use of chemistry-derived tools play an analogous role in development and evolution of biological theories? This special issue of Chemistry & Biology is dedicated to exploring this question and includes an exciting collection of articles focusing on applying chemical tools to the study of biology.

Before proceeding with more details of the topics covered in the 2010 Special Issue of Chemistry & Biology, I would like to thank, on behalf of the entire editorial group, the authors who contributed their exciting articles, all of the reviewers who provided valuable feedback, and the many other scientists consulted during the preparations for this issue, as well as to emphasize that this special issue is the result of a true collaborative effort among the many researchers involved.

As the journal that aims to serve as an intellectual bridge between the chemical and biological communities, we hope that the selections of topics and articles included in this issue will serve to inform and to intrigue, to educate and excite, and, above all, to encourage more to cross the bridge and explore that unique opportunities that arise from applying chemical probes to biological questions.

Bullets for the Undruggable Proteome

PAGE 551

If you were to dream about the small molecules of the future, what would be their powers be? In a crosstalk article included in this issue, Craig Crews provides his answer to this question and discusses the issues that small molecule probe development efforts are currently facing as they challenge the idea of the "undruggable proteome."

Five Molecules for a Remote Island

PAGE 556

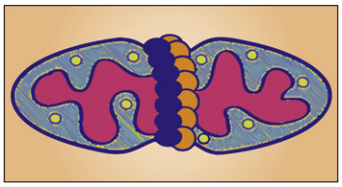
If you could take just five small molecules to a desert island, what would they be? We asked Thomas U. Mayer and Andreas Marx this question, and in their crosstalk article, they provide a list of the five molecules not to be left behind when packing.

How Fit Is Your Probe?

PAGE 561

Cell-permeable small molecule probes have a major role in facilitating our understanding of physiological and pathological processes and in validating new drug targets. Recent publications have suggested objective guidelines for what makes a useful chemical probe. While recognizing that guidelines may be valuable, Paul Workman and Ian Collins, in the perspective included in this issue, caution against overly restrictive rules that may stifle innovation in favor of a "fit-for-purpose" approach. By reviewing the literature and providing examples from the cancer field, they recommend a series of "fitness factors" to be considered when assessing chemical probes. This approach should encourage innovative chemical biology research while minimizing the generation of misleading biological data.

Studying Mitochondrial Division



PAGE 578

An increasing number of diseases are associated with excessive mitochondrial division, such as Alzheimer's disease, Parkinson's disease, and diabetes, and this link makes proteins involved in mitochondrial division attractive targets for therapeutics. In their minireview, Laura L. Lackner and Jodi Nunnari discuss a small molecule inhibitor of mitochondrial division, mdivi-1, and how the use of this inhibitor has provided valuable insight into the mechanism of mitochondrial division and shown great therapeutic promise in a wide array of disease models, demonstrating the potential of a new class of therapeutics that target mitochondrial division.

Wanted: Regulators of RNAi/miRNA

PAGE 584

RNA interference (RNAi) is a well-conserved mechanism that uses small noncoding RNAs to silence gene expression posttranscriptionally. A minireview by Peng Jin and colleagues highlights recent discoveries of small-molecule modulators of the RNAi/miRNA pathway that illustrate how a chemical biology approach could be used to dissect the RNAi/miRNA pathway.

Chemistry Not Arresting the Development

PAGE 590

Creating a complex multicellular organism from a single zygote requires an ensemble of cellular and molecular events that unfold with spatiotemporal precision. While developmental biologists have traditionally investigated these processes through surgical and genetic manipulations, chemical technologies are increasingly being used to achieve a dynamical understanding of embryonic patterning mechanisms. In this review, Xiaohu Ouyang and James K. Chen examine how synthetic strategies have illuminated the roles of gene expression, protein function, and cell physiology during embryogenesis. The authors also discuss current challenges and future opportunities at the crossroads of chemistry and developmental biology.

Neuronal Activity under Control

PAGE 607

How does neuronal activity code for perception, emotion, thought, and behavior? New technologies offering precise spatiotemporal control over neuronal activity are poised to answer this question. Inspired by key control points in neuronal signaling (membrane potential,

neurotransmitter release, postsynaptic receptor activity), these technologies utilize light and/or small molecules to control the activity of exogenous proteins expressed in genetically defined populations of neurons. The control points and the technologies developed to rapidly and reversibly manipulate them are reviewed here by Pamela England.

Right Tool for the Job

PAGE 616

Understanding the mode of action of small molecules is critical for fully exploiting their use as both target-specific probes of biological function and potent therapeutic agents. In this review, Motonari Uesugi and colleagues discuss affinity-based isolation of molecular targets of bioactive small molecules. The method is considered to be one of the classic approaches for tackling this problem and the review, intended to be both an update on the most recent findings for those already active in the field of forward chemical genetics and a guide for scientists entering this burgeoning field, highlights its power and discusses potential limitations.

Chemical Genomics View of Microbial World

PAGE 624

A review by Eric D. Brown and colleagues describes current chemical genomic methodologies used to study the biology of model microbial systems. Specifically, the authors highlight the effectiveness of using small molecules as perturbants of biological systems and discuss an array of genomic and chemical tools to this end, including genome-scale clone sets, microarray- and promoter-based transcriptional profiling, chemical proteomics, and computational approaches. The review emphasizes the utility of these approaches in developing our understanding of cellular complexity. Further, the review highlights the importance of these methods to the identification and thorough understanding of modes of action of new probes of biology and new leads for drugs.

Interpreting Translation One Antibiotic at a Time

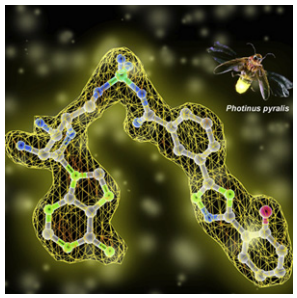
PAGE 633

The main antibiotics currently in use target bacterial translational apparatus, and for a number of them, the details of their mechanisms of action are well understood. In their review, Daniel N. Wilson and colleagues discuss how studies of antibiotics' mechanisms of action have often led to important and sometimes unexpected insights into many fundamental aspects of the translation mechanism. Key breakthroughs in the field, such as crystal structures of the bacterial ribosome, together with recent developments in single-molecule and fast-kinetic approaches, provide an integrated view of the dynamic translation process and have the potential not only to accelerate the discovery of novel and effective antimicrobial agents, but also to refine our understanding of the translation mechanism.

Light at Dark Places

PAGE 646

Understanding luciferase enzymology and the structure of compounds that modulate luciferase activity can be used to improve the design of luminescence-based assays. The review by Douglas S. Auld and colleagues focuses on bioluminescent reporters used in high throughput screening (HTS) with emphasis on *Photinus pyralis* firefly luciferase (FLuc). The authors discuss chemical structures that inhibit FLuc and the mechanism of inhibitor-based reporter stabilization, formation of potent inhibitors by non-light-emitting reactions catalyzed by FLuc, as well as implications for the interpretation of luciferase reporter assays. (Figure credit: Auld et al.)



Finding the Target for an Orphan Compound

PAGE 659

Using chemical proteomics and pharmacological approaches, Fleischer et al. identify nicotinamide phosphoribosyltransferase (Nampt) as the target of CB30865, a potent cytotoxic compound of previously unknown mechanism of action. CB30865 analogs were shown to specifically bind to and inhibit Nampt with nanomolar potencies both in vitro and in cellular mechanism-based assays. Cellular effects and cytotoxicity of CB30865 analogs were prevented by nicotinic acid as an alternate source of NAD. These results unequivocally substantiate Nampt as the unknown target of CB30865 analogs and suggest a new chemical core for Nampt inhibitor development. Furthermore, the results underpin the utility of chemical proteomics in target identification.

Images of Zincking Brain

PAGE 665

Construction of cell-permeable contrast agents for MRI is a significant challenge. Here, Lee et al. show that a porphyrin-based MRI molecular imaging agent, Mn-(DPA-C_2)$_2$-$TPPS_3$, effectively penetrates cells and persistently stains living brain tissue in intracranially injected rats. Optical absorbance of the probe also permitted direct visualization of its distribution by histology. The imaging agent was designed to sense zinc ions, and contrast enhancement was more pronounced in a zinc-rich brain area than in a second region that contains relatively little labile Zn^{2+}. Membrane permeability, optical activity, and high relaxivity of porphyrin-based contrast agents offer exceptional functionality for in vivo imaging.

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